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CANCER OF THE BREAST: THE SURGEON'S DILEMMA

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SUDDENLY, after 50 years of complacent acceptance of radical mastectomy, the surgical world is plunged in doubt. On the one hand, Urban and Baker[1] and Wangensteen[2] advocate extension of the radical operation to include resection of the internal mammary nodes; on the other, there is mounting evidence that simple mastectomy gives better results than the conventional radical operations.[3]

Since even in the most skillful hands the conventional radical mastectomy may cause disfigurement and dysfunction, it is important to determine whether it is really necessary to employ it routinely. To date there is no proof that the results of radical mastectomy are better than those of simple. Pathologists may theorize on the rationale of eradicating cancer by extended surgery,[4] but in the final analysis it is the survival of patients that counts. So little is known about the ways of cancers and the complex relationships of tumors to their hosts that theoretical considerations based on the traditional concept of the spread of cancers are of little value.

In the traditional concept of the spread of cancer, the tumor is at first localized, later spreads to the regional lymph nodes, and finally throughout the body. According to this concept the most extensive operation performed at the earliest possible moment should give the best chance of cure.

In opposition to this concept is the theory that Gatch[5] has long held and that MacDonald[6] has named *biologic predeterminism*. In this concept, the course of the disease is thought to depend chiefly upon the biologic properties of the tumor and the resistance of the host. In cancer of the breast, the principle of biologic predeterminism is sustained by the studies of Park and Lees[7] which indicate that it is impossible to prove that the course of cancer of the breast is influenced by any form of surgical treatment.

The present crisis in our thinking about cancer of the breast was precipitated by McWhirter[8] in Edinburgh, Scotland, who subjected a population group of more than a million people to a careful clinical experiment. All cases of cancer of the breast that occurred in this population group were included, regardless of how they were treated, or whether they received no treatment at all. Ackerman,[4] who reviewed McWhirter's material, did not agree with McWhirter's conclusions but had little criticism of the basis for the diagnosis or of the completeness of the follow-up.

In the United States the results of McWhirter's experiment have been widely misunderstood. Many surgeons believe that McWhirter showed that irradiation is as effective as radical mastectomy. Nothing could be farther from the truth. McWhirter's results indicate that although irradiation controlled local recurrences, it had little effect upon the survival of patients with cancer of the breast. The chief significance of the Edinburgh experiment is that it suggests that in some cases radical mastectomy may *shorten* the period of survival. In all operable stages of the disease, McWhirter found that the results of simple mastectomy were superior to those of radical mastectomy.

McWhirter's study is divided into three five-year periods. In the first period, the majority of the operable cancers were treated by *radical* mastectomy. In the second period, postoperative irradiation was added. In the third period, most of the operable cancers were treated by *simple* mastectomy and irradiation. In order to eliminate factors of selection, the results in each of these successive periods were listed under the type of treatment that predominated during that period, so that in the group considered to have been treated by simple mastectomy and irradiation there are some patients who had no treatment, some who had only irradiation, and some who had radical mastectomy, but most had simple mastectomy and irradiation.

McWhirter found that roentgen therapy given after radical mastectomy reduced the incidence of local recurrences but made no significant change in the survival rates. However, when the treatment was changed from radical mastectomy to simple mastectomy, irradiation being given in both instances, the survival rates at five and at ten years after operation were increased by more than 10 per cent. From this experiment McWhirter has drawn two conclusions: (1) that in many cases irradiation can control local recurrences, and (2) that by not dissecting the axilla, dissemination of disease is avoided and the survival rate is increased.

It is interesting that from an opposite approach, with emphasis on meticulous and extended operations, Haagensen and Stout[9] are working toward identical conclusions. They now emphasize the desirability of taking biopsies of mediastinal and supraclavicular lymph nodes before performing a radical mastectomy, and advise that if these nodes are involved, treatment should be solely by irradiation. Their results with this method of treatment are reported to be excellent, because they do not operate on the types of cancer that operations are apt to spread.

There is mounting evidence that the regional lymph nodes, even when

involved by cancer, may act more often as a barrier to further spread than as a source of dissemination. Williams, Murley, and Curwen[3] at St. Bartholomew's Hospital in London, England, analyzed the results of various types of operations that were performed 25 years ago during the height of the vogue for radical mastectomy. Fortunately there was one surgeon, Sir Geoffrey Keynes, who treated a large number of cancers by local excision, local implantation of radium needles or by simple mastectomy, but almost never by radical mastectomy. The survivals of his patients were longer than those of the surgeons who did radical mastectomies, and Williams, Murley, and Curwen concluded that with or without irradiation, simple mastectomy gave better results than radical mastectomy at St. Bartholomew's Hospital.

A similar report in this country by Meyer and Smith[10] shows that the results of simple mastectomy done on unselected cases in a community hospital were slightly better than those of the conventional radical operation (the five-year survival rate was 8 per cent higher). Small and Dutton[11] at the University of Rochester came to similar conclusions. Byrd and Conerly[12] at Vanderbilt University analyzed the survival rates of women who were aged, debilitated, or had advanced cancer, and who had undergone simple mastectomy, and compared these survival rates with those of women who had undergone radical mastectomy. They found that in the clinical stage I cases with no palpable involvement of the axillary nodes, the survival rates were slightly better after the simple than after the radical operation. Despite the more advanced stage of the disease in the clinical stage II cases treated by simple mastectomy the survival rates after simple mastectomy were remarkably similar to those after the radical procedure done in a more favorable group of cases. Finally, Deaton[13] in a survey of the world literature, reported that the survival rate following simple mastectomy was 5 per cent higher than that following radical mastectomy.

These observations are disturbing to our conventional thinking about cancer, and cannot be explained without drawing an analogy between the role of the lymph node in infection and in cancer. In an infection of the hand we view the axillary nodes as a barrier to systemic spread. We treat the local lesion and count on the natural resistance of the body to overcome the bacteremia and the lymph-node involvement. Surgeons have learned from bitter experience that they spread the disease if they excise lymph nodes that are involved by virulent infections. Yet in grade IV cancers, when blood vessels and lymphatics are filled with tumor cells, many surgeons do not hesitate to excise the lymphatic barrier.

The dissemination of cancer cells into the blood stream is much more common than we have realized. In 59 per cent of a series of 107 cases of operable cancers of the breast, lung, stomach, and colon, Engel[14] of Stockholm, Sweden, found cancer cells free in the blood of the veins that drained the cancers. Thirty-five per cent of grade II cancers had cells in the blood, 78 per cent of grade III, and 100 per cent of grade IV.

The two properties of cancer cells that enable them to enter the blood stream are their lack of attachment to surrounding cells and their ability to migrate by ameboid movement. These properties account for the exfoliation of living cells

that makes possible the Papanicolaou smear test for cancer of the cervix. The same properties cause internal migration and exfoliation of cells into the streams of body fluids. As Denoix[15] of Paris, France, has said, there probably is a time in the evolution of all cancers when they are systemically disseminated. The spread of the cancer therefore depends much more upon the resistance of the host and the ability of the circulating cells to implant and to grow than upon the type of surgical treatment.

Although we can avoid unnecessary manipulation of a cancer and although in some situation we can ligate the veins that drain a cancer before we disturb it, there is little else that we can do to prevent dissemination of cancer through the blood stream. But perhaps we can avoid its widespread dissemination through the lymphatics. The experiments of Zeidman and Buss[16] who injected cells of a transplantable cancer into the popliteal lymphatics of chickens, indicate that lymph nodes are effective barriers to the spread of cancer and localize the disease for long periods of time. This evidence should encourage us to study further the possible advantages of performing the initial operation for cancer of the breast within the lymph-node barrier.

The principle of local excision or destruction of a cancer within the lymph-node barrier has been employed for many years in the treatment of cancers of the lip, skin, and mouth, where treatment of clinically uninvolved lymph nodes often is deferred until the course of the disease can be evaluated. The advantage of simultaneous or prophylactic resections of lymph nodes in these cases never has been established. Indeed, in the treatment of some tumors such as melanoma, the opposite may be true. The survival rate following simultaneous dissection of the primary melanoma and palpable lymph-node metastases is almost nil, yet nearly half of the patients have been reported to survive more than five years when the primary is first removed and involved nodes are resected at a later operation.[17] In patients with lymph-node involvement from highly malignant tumors, it may be that the lymphatics are filled with cancer cells on their way to the lymph nodes. If so, wide resection of the nodes, before the primary tumor has been removed and before the cells in the lymphatics have been fixed or destroyed by the forces of body resistance, may disseminate the tumor more widely. In such cases, the challenge to the surgeon is much the same as it is in the treatment of infection. It is not so much to operate as early and as widely as possible as it is to determine as early as possible which lesions are adapted to surgical treatment.

Even more important than technical considerations of the lymph-node barrier are the biologic considerations of the cancer's growth. If we had some way to recognize, before operation, the pattern of the tumor's growth and spread we could avoid many of the dangerous operations that disseminate disease. At present there are only two ways of estimating preoperatively the biologic potential of a cancer. One is by observing its response to radiation therapy, the other is by observing its clinical course.

The response to irradiation is used by MacDonald[18] as an index of the operability of breast cancers. In clinical stage II cancers, in which axillary nodes

are palpable, he gives 1800 r over a period of two weeks, and if the nodes decrease in size by one third or more he considers the cancer to be biologically better adapted to irradiation than to surgery and relies solely on irradiation in the treatment of the metastases. If, on the other hand, there is little or no response, he performs a conventional radical mastectomy. Similar principles are being tested by the Grahams[19] in their use of the factor of radiation sensitivity in selecting cancers of the cervix for treatment by irradiation or by surgery.

An alternative biologic approach is to use the factor of time as an index of the tumor's biologic behavior. In this system the initial treatment of a clinical stage I cancer of the breast with no palpable nodes would be simple mastectomy or, occasionally, in carefully selected small peripheral lesions, wide local excision. The axilla is then periodically examined. If in a few months diffuse involvement of axillary nodes becomes apparent, intensive cobalt teletherapy is given. If systemic metastasis is apparent, endocrine therapy is tried. If, on the other hand, two or three years elapse before one or two movable nodes become palpable it is assumed that the resistance of the body to the tumor is high and that the tumor is better adapted to control by radical axillary dissection than by irradiation.

In clinical stage II cancers with palpable axillary nodes, if the history is short, the treatment is simple mastectomy and irradiation by the McWhirter technic. But if the patient states that the primary tumor has been present a year or more, if it is located in the upper outer quadrant, and if the palpable nodes are few and movable, radical mastectomy is performed.

Since there is evidence that irradiation may do harm as well as good, I believe that irradiation should not be applied prophylactically as a routine measure. The balance between the growth of the tumor and the resistance of the host is a delicate one that can be tipped easily in either direction. In experimental animals, Kaplan and Murphy[20] have shown that irradiation of radiation-resistant tumors is apt to hasten their metastasis, and Krebs[21] has found that irradiated cancers invade more extensively than do nonirradiated controls. Clinically too, a tumor sometimes seems to grow and spread more rapidly after irradiation, as for example in one of my patients in whom a local recurrence of a breast cancer treated by irradiation grew through the chest wall and pericardium and into the myocardium.

Even endocrine therapy is not without danger. Adrenalectomy, as Moore[22] has shown, may stimulate the growth of a cancer of the breast. Administration of androgens also may accelerate its growth.[23] Even oophorectomy is not free of this danger and should not be applied indiscriminately. In young women there are breast cancers that are in no way dependent on estrogens, but rather are dependent on the growth or on the mammotropic hormones of the pituitary, which may be cross-stimulated by oophorectomy. I have seen such a cancer in a menstruating woman, 42 years old, whose cancer grew more rapidly after roentgen sterilization of the ovary and then went into a striking remission when she was given desiccated thyroid, cortisone, and 20 mg. of stilbestrol daily to suppress the activity of the pituitary.

Apparently, with the possible exception of removal of the pituitary, there are no operations, no technics of irradiation, and no treatments with sex hor-

mones that are free of the risk of accelerating the growth of cancer of the breast. For the present, therefore, and until we develop a better understanding of the factors that control the spread of cancer, it may be best to avoid therapeutic generalizations and to base treatment on the biologic behavior and response to treatment of the individual cancer.

Summary

1. Since we know little of the factors that influence the spread of cancer, no valid generalizations can be made about the treatment of cancer of the breast.

2. At present there is no basis for advocating any single type of operation for operable cancers of the breast and there is no basis for employing a general policy, pro or con, regarding irradiation, removal of endocrine glands, or endocrine therapy.

3. Each patient with a cancer of the breast should be considered as an individual problem and treated according to the biologic behavior of the tumor and the resistance of the host.

4. Since there is doubt whether any of our treatments will often prevent the distant spread of cancer, a heavy burden of responsibility rests on the surgeon. The day is past when he can accept the credit for prolonged survival and consider himself free of responsibility if after the treatment the cancer spreads.

5. Surgery, irradiation, and endocrine therapy are double-edged swords that may harm as well as help.

6. The challenge to the surgeon is to control the cancer as well as possible and to do so with the least possible harm.

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ACHALASIA OF THE CARDIA AND MEGA-ESOPHAGUS

Report of Five Representative Cases

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ACHALASIA, defined as failure or inability to relax, when applied to the esophageal cardia most accurately designates a familiar clinical and pathologic disease entity. The term *mega-esophagus* refers to the presence or development of a dilated esophagus in association with achalasia of the cardia, and must be so restricted. Less acceptable in the light of present knowledge is the older term *cardiospasm*, which has been defined as a functional type of obstruction of the esophagus at or near the esophageal hiatus, usually associated with dilatation of the thoracic esophagus.[1] Effler and Rogers[2] differentiate cardiospasm from mega-esophagus, but the two conditions may be essentially the same, differing only in degree and duration. We have seen patients with achalasia without esophageal dilatation who later developed mega-esophagus.

The purpose of this paper is to review briefly the etiology, clinical features, and treatment of achalasia and mega-esophagus, and to present the reports of five cases that demonstrate the diagnostic findings, the treatment, and some of the complications of the condition.

Etiology

The etiology of achalasia is not known. It rarely is associated with gross organic disease of the esophagus. Most proposed explanations of the etiology have focused on the nervous control over the lower esophagus. Hurst[3] in 1930 reported that some patients with achalasia had degenerative changes in Auerbach's plexus in the lower esophagus. He observed that the abdominal esophagus failed to relax in front of the contractional wave. Knight[4a] in 1934 experimentally reproduced this condition in cats by high bilateral vagotomy. He also was able to prevent or to relieve the condition experimentally by sectioning the sympathetic nerve supply to the cardiac end of the stomach and lower esophagus. He[4b] later employed left gastric sympathectomy in the treatment of some patients with achalasia and reported good results in a few. Mitchell[5] and others

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have noted that sympathetic denervation of the cardia is an extensive and impractical procedure in human beings.

Etzel[6] in 1942 reported that mega-esophagus frequently was associated with vitamin B_1 deficiency. He found that other conditions, including megacolon, megaureter, pyloric achalasia, altered intracardiac conduction, low basal metabolic rate, and polyneuritis, frequently coexisted with mega-esophagus. He attributed these changes to degeneration in Auerbach's plexus involving the digestive and urinary tracts. He believed that this degeneration resulted from deficiency in vitamin B_1 because that deficiency was present in 626 patients having mega-esophagus included in a survey.

Mega-esophagus and megacolon are similar in that each involves dilatation and atony of the respective organ proximally, and may involve degeneration of Auerbach's plexus. A true *cardiospasm* rarely is present in patients having mega-esophagus, and hypertrophy of the muscle at the cardiac sphincter, such as that which occurs in congenital hypertrophic pyloric stenosis, seldom is seen. The term *achalasia* describes the deranged neuromuscular mechanism in mega-esophagus better than does *cardiospasm*. The pathologic changes probably are not restricted to the distal esophagus, since extremely ineffective and tertiary peristalses and atony are present throughout the esophagus. Palmer[7] states, "Achalasia is a disease of the esophagus as a whole. In a sense the abnormality at the cardia is least important. Atony of the upper esophagus with absence of peristaltic activity is of primary importance." He reports that achalasia is much more common than cardiospasm.

There are a number of factors that may result in degeneration of Auerbach's plexus and achalasia and mega-esophagus. These include congenital absence of the plexus, vitamin B_1 deficiency as reported by Etzel,[6] syphilis and other neurologic lesions, emotional factors, circumscribed lesions in the lower esophagus, reflex irritation from ulcer and other diseases, and allergy.

Clinical Features

The diagnosis of achalasia of the cardia is based upon the history and the roentgen and esophagoscopic findings.

Initially the patient may complain of slight pain, pressure, discomfort or burning at or near the xiphoid, or a sensation of food lodging in the lower esophagus after swallowing. The symptoms initially may be intermittent. Occasionally there may be an abrupt onset. The symptoms become progressively more severe and frequent until the retrosternal pain becomes continuous and severe. Attacks of distress may be precipitated by rough foods, cold fluids, acute infections, and emotional tension.

The pain may be referred to the neck, jaw, or ears, and may closely simulate angina pectoris in character and distribution, but is not related to exertion. With balloon studies and distention of the esophagus, anginoid type of pain and electrocardiographic changes have been shown to be associated with esophageal spasm.

Late in the course of achalasia, usually after dilatation of the esophagus has occurred, there may be a great loss in weight, a hypochromic anemia, and symptoms of vitamin deficiencies due to poor nutrition. Regurgitation of undigested food may occur. Pulmonary symptoms of cough and dyspnea may result from the pressure of a greatly distended esophagus, or from aspiration pneumonitis and bronchitis that are caused by repeated aspiration of undigested food during sleep.

Roentgen examinations show varying degrees of dilatation of the esophagus with retention of food. The esophagus may be so greatly dilated that a diagnosis of mega-esophagus can be made on roentgen study of the chest alone. Barium swallow shows the esophagus tapering to a smooth constriction at the level of the hiatus; this constriction is characteristic of achalasia. The margins of the esophagus are smooth and regular. Fluoroscopic examination usually shows an atonic dilated esophagus with weak, ineffective tertiary waves and no primary peristalses. Esophagoscopy is indicated to exclude the possibility of organic lesions of the distal esophagus.

Complications that may result from achalasia include esophagitis which usually is present with mega-esophagus, stasis of food, ulcerations and erosions in the esophagus, aspiration pneumonitis, and pulmonary abscess. Spontaneous pneumothorax following the Valsalva maneuver,[8] pleural effusion,[9] bronchiectasis,[10] and fistulous communication with a bronchus[11] also have been reported. Carcinoma of the esophagus is uncommon in patients with achalasia, although three such cases have been reported.[1]

Treatment

The treatment of achalasia is essentially medical with esophageal dilations, bland diet, and supportive measures. Surgery is reserved for the patient whose condition does not respond to medical treatment. We agree with Bockus,[1] that "All physicians who have had some experience with cardiospasm, believe that surgical operation of any type is contraindicated unless all methods of peroral dilation have failed."

The basic principle of the medical treatment of achalasia is dilation of the cardiac sphincter. Various types of dilators are used, including hydrostatic and pneumatic dilators and mercury bougies. The dilators can be placed in position under fluoroscopic control; sufficient pressure must be used to disrupt some of the muscle fibers. One dilation may suffice, but frequently several are required. Some of our patients have learned to pass dilators themselves, and to perform dilation whenever their symptoms recur. One of Sippy's principles was that where water would pass, a string could be passed, and where a string would pass, a dilator could be passed over the string. The first dilation may be done at the time of esophagoscopic examination.

Supportive measures are important and may be quite helpful. A bland, high-caloric, high-protein diet is recommended, and excessively hot and cold fluids should be avoided. Sedation may be helpful, but atropine, belladonna, and

anticholinergic drugs are contraindicated, because Knight[4a] reproduced this condition in cats with a high vagotomy. Adrenolytic drugs may be of some help. Local anesthetic agents, such as procaine or Probutylin-Rorer, before meals have been of help in some patients. Large doses of vitamin B should be given not only because of the possibility that deficiency in B_1 is a factor in etiology but also because many of these patients are deficient in the entire vitamin B complex. Aminophyline and nitroglycerin have been used with beneficial effect in a few patients.

Sifers and Crile[11] reported a follow-up study of 92 of 100 patients with cardiospasm and found only 18 failures on medical treatment, including dilations. Four of these 18 patients were successfully treated by surgical intervention.

Most of the patients in whom surgery is necessary have severe symptoms of mega-esophagus. Regurgitation, particularly if it occurs during sleep, with resulting cough, dyspnea, and aspiration pneumonitis, is an indication for surgery. Persistent anemia and malnutrition that do not respond to medical treatment are indications for surgery. It should be pointed out that surgical myotomy is very similar to medical dilation in that the circular muscular fibers are interrupted in both procedures. The size of a dilated esophagus rarely returns to normal after any surgical procedure, which is another indication that achalasia is a disease affecting the entire esophagus.

Effler and Rogers[2] believe that linear myotomy is the preferred operation and report good results for 20 patients who underwent that procedure. Sweet[12] reported his findings in a series of 48 patients who had undergone surgery for this condition. He divided his patients into two groups. Patients in group I did not complain of pain, but had dysphagia, malnutrition, and severe mega-esophagus; Sweet reported 80 to 100 per cent improvement in 13 of the 20 patients in this group treated by esophagoplasty. Patients in group II complained of substernal pain and had only moderate dilatation of the esophagus; at operation the circular muscle of the lower segment in these patients may be found to be thickened. In group II, Sweet prefers a linear myotomy, and reports a 90 to 100 per cent improvement in seven of seven patients after this procedure. Microscopically, degeneration of Auerbach's plexus was apparent in the patients in both of Sweet's groups.

Case Reports

The following selected cases demonstrate many of the clinical manifestations and complications of achalasia, and the indications for and results of medical and surgical treatment.

Case 1. A 24-year-old woman was first examined here in September 1949. She had a four-year history of substernal pain after meals which was frequently relieved by the drinking of water. For the six months preceding examination she had some regurgitation of undigested material, particularly during sleep. The patient volunteered the information that the symptoms were aggravated by rough foods and by emotional strain.

The findings on a complete physical examination were normal. Laboratory studies showed that the hemoglobin content was 12.2 grams per hundred milliliters, the serum albumin 4.8 and the serum globulin 3.6 grams per hundred milliliters. The remaining laboratory studies including urinalysis, serology, and determination of blood sugar level and basal metabolic rate were normal.

Roentgenograms of the chest were normal. Barium swallow revealed a typical cardiospasm with a funnel-like deformity at the cardiac end where the esophagus was approximately twice its normal width. No primary peristaltic waves were present.

On September 13, Hurst dilators, numbers 36 to 60, were passed and then a mercury bag was passed and inflated to 15 pounds for five minutes. After the dilation, the patient was given a bland diet, sedation, and vitamin B.

Subsequently, the patient's condition progressed satisfactorily. On April 10, 1956, approximately six years after initial examination, the patient's family physician reported that the patient had little or no dysphagia and only occasional episodes of epigastric burning; additional dilations had not been necessary.

Comment: This patient's condition responded satisfactorily to one dilation; however, several dilations frequently are required. The satisfactory progress of this patient's condition for a period of six years certainly indicates that surgery was unnecessary.

Case 2. A 33-year-old woman was first examined here on April 26, 1947, because of a one-year history of nausea, vomiting, and loss of 65 pounds in weight. For the year preceding examination, she also had difficulty in swallowing bread and other solids, and noted flatus, belching, bloating, retrosternal pain, dyspnea, and regurgitation of undigested food during sleep.

On physical examination the patient's weight was 118 pounds; the tongue was coated and dry and the buccal mucosa showed some desquamation. The remainder of the findings on physical examination and laboratory studies were normal. Barium swallow showed that the esophagus was enormously dilated throughout its entire length, and that the distal esophagus was cone-shaped (Fig. 1).

Esophagoscopy revealed that the esophagus was filled with food. No evidence of neoplasm was found when an esophagoscope was passed into the cardia. The patient underwent repeated esophageal dilations with mercury bougies inflated to 15 pounds. During the three months after initial examination she gained 22 pounds in weight.

The patient was next seen in May 1950, approximately three years after the initial examination. She weighed 204 pounds (a weight gain of 86 pounds in the three years). Her only complaint was that food occasionally lodged in the esophagus, particularly when she was not relaxed while eating. Barium swallow showed that the esophagus was less dilated than it had been in 1947. Constriction at the distal end was smooth and tapering, characteristic of cardiospasm. She was given a reducing diet, and during the next three months she lost 18 pounds in weight.

Approximately one year later, in July 1951, the patient was asymptomatic but she weighed 213 pounds. The findings on barium swallow were essentially the same as those in 1950. One esophageal dilation was performed.

When the patient was last seen in October 1954, seven and one-half years after initial examination, she still was asymptomatic. She weighed 206 pounds. Findings on complete physical examination, laboratory studies and roentgenogram of the chest were normal. Barium swallow showed no change in the appearance of the esophagus.

Comment: This patient had a one-year history of dysphagia, retrosternal pain, regurgitation of undigested food, vomiting, dyspnea, and loss in weight. A series of esophageal dilations resulted in regression of the symptoms and gain in weight of 95 pounds. She has remained asymptomatic for seven and one-half years, although the esophagus still

Fig. 1. (Case 2) Esophagograms. **A.** Obtained in 1947. Large dilated atonic esophagus tapered at the cardia, consistent with a diagnosis of achalasia. **B.** Obtained in 1950. The esophagus is less dilated than it was in 1947 (A), and some return of tone to the wall is evident. **C.** Obtained in 1954. The esophagus still is somewhat dilated, but the dilatation is less than that in 1947 (A).

A B

Fig. 2. (Case 3) **A.** Esophagogram showing dilated esophagus typical of achalasia. In patients with carcinoma of the esophagus, this extreme degree of dilatation is seldom seen. **B.** Spot film showing the tapered appearance of the lower end of the esophagus, which is typical of achalasia.

is dilated. When the esophagus becomes dilated to the extent that it was in this patient, medical or surgical treatment seldom can relieve the dilatation. However, this patient's condition responded well to one series of dilations, which indicates that dilatation of the esophagus in itself is not sufficient indication for surgery, since medical treatment may accomplish, as in this patient, everything that surgery would be able to do.

Case 3. A 42-year-old man was first examined here on November 15, 1951, because of a three-month history of a tickling cough in his throat, gagging, and vomiting. His symptoms were most distressing at night; he would awaken with a cough, have a small emesia, and then be comfortable for the rest of the night. For the previous ten years he had had some difficulty in swallowing solid food. The patient had no other respiratory symptoms and he had not lost weight.

Findings on physical examination were normal except for a mucopurulent nasal discharge. Laboratory examinations including urinalysis, serologic tests for syphilis, and determinations of blood count and blood sugar level were normal.

On roentgen examination, the chest was normal, but the esophagus was found to be dilated to a diameter of approximately 5 cm., with a smoothly narrowed and tapered distal esophagus (Fig. 2).

Esophagoscopy revealed fluid retained in the esophagus. There was a smooth narrowing of the esophageal hiatus, with no evidence of neoplasm. Esophageal dilation with a French no. 60 dilator was performed, and the patient was given a bland diet, sedation, and vitamin B complex.

The patient was last seen in February 1954, approximately three years after initial examination, at which time a thyroid adenoma was removed. He was asymptomatic in regard to the achalasia, although barium swallow showed no essential change in the appearance of the esophagus. The patient reported by letter in June 1956 that he had remained asymptomatic.

Comment: This patient had a ten-year history of mild dysphagia, and a three-month history of coughing, gagging, and vomiting at night. A diagnosis of achalasia and mega-esophagus was made. He has remained asymptomatic after one esophageal dilation.

Case 4. A 34-year-old woman was first examined here on June 30, 1954, with presenting complaints of vomiting, thoracic pain, and a weight loss of 60 pounds during the previous two years. She had frequently regurgitated during sleep, and she had difficulty in swallowing, particularly of solids. Thoracic pain was severe and relatively constant, but it was relieved by vomiting. Two esophageal dilations performed elsewhere, four and seven months previously, had partially relieved the symptoms. For two months preceding our examination the patient had been aspirating herself at bedtime with an Ewald tube with some relief.

Findings on physical examination were essentially normal. Laboratory studies including urinalysis, serologic tests for syphilis, and determinations of blood count, blood sugar level, serum proteins, and prothrombin time were normal.

Barium study of the esophagus revealed a smooth narrowing at the cardia with proximal dilatation to a diameter of 8 cm. (Fig. 3). Food and barium were retained in the esophagus at the end of two hours. Esophageal dilation with a no. 60F Hurst mercury bougie was performed, and the patient was placed on a bland diet with supplemental nourishment, sedation, and an adrenolytic medication; also the head of her bed was elevated eight inches. Initially, moderate improvement in the patient's condition was noted, but there were frequent aspirations at bedtime, and she continued to have pain in the chest, regurgitation during sleep, and some coughing.

The presence of aspiration pneumonitis made surgery advisable. On September 1, 1954, approximately two months after initial examination, a linear myotomy was

Fig. 2. (Case 3) **A.** Esophagogram showing dilated esophagus typical of achalasia. In patients with carcinoma of the esophagus, this extreme degree of dilatation is seldom seen. **B.** Spot film showing the tapered appearance of the lower end of the esophagus, which is typical of achalasia.

performed; the postoperative course was uneventful. The coughing and vomiting subsided and the patient gained 38 pounds in weight. Postoperative barium swallow showed that the diameter of the esophagus had decreased from 8 to 5 cm. (Fig. 4). A year later, in September 1955, she became pregnant. When she was last examined in April 1956, approximately two years after her initial visit, she was asymptomatic concerning the achalasia, and was tolerating her pregnancy satisfactorily.

Comment: This patient had a two-year history of dysphagia, vomiting, regurgitation, cough, thoracic pain, anorexia, and loss in weight. She failed to respond to medical treatment with dilations, continuing to have the thoracic pain, regurgitation during sleep, cough, and evidence of aspiration pneumonitis. After linear myotomy, she became asymptomatic. There was some decrease in the size of the dilated esophagus postoperatively; it is unusual for mega-esophagus to decrease in size after either medical or surgical treatment. Surgery is indicated when, despite medical treatment, thoracic pain and respiratory symptoms, frequently due to aspiration pneumonitis, persist. Surgery should

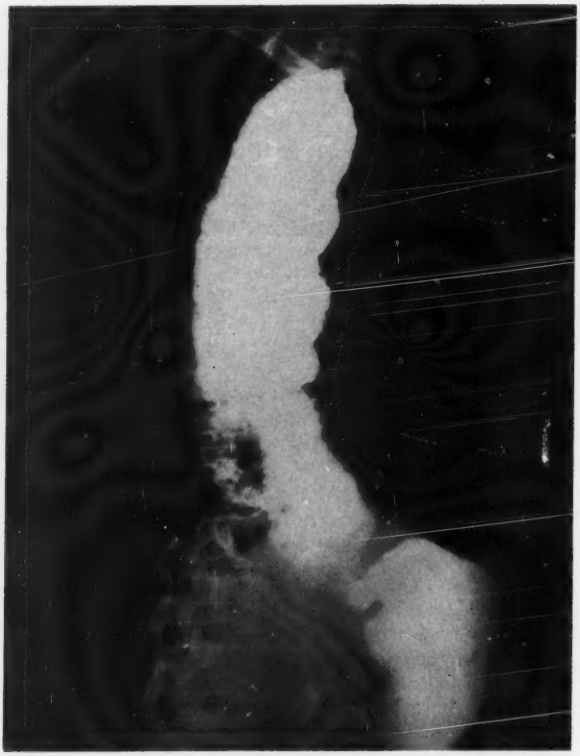

Fig. 3. (Case 4) Preoperative esophagogram showing moderate mega-esophagus and lack of tone. Surgery was performed because of persistent malnutrition, regurgitation, and aspiration pneumonitis, despite medical treatment including dilations.

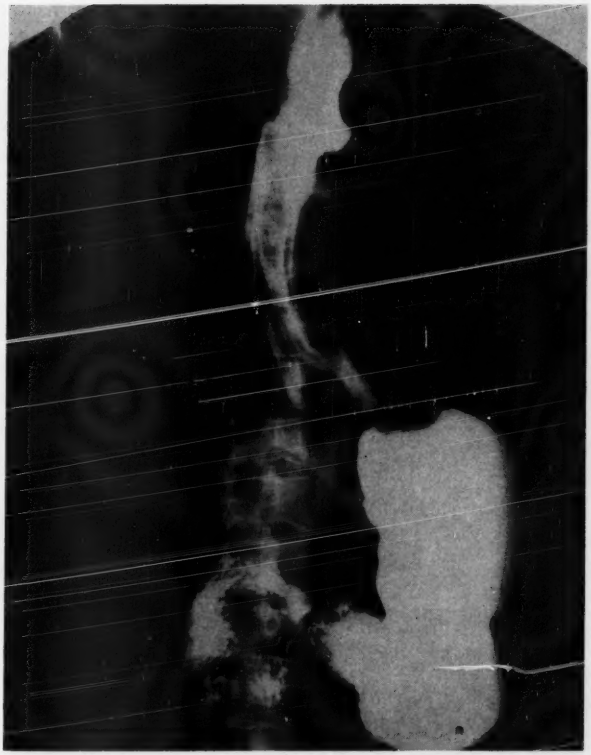

Fig. 4. (Case 4) Postoperative esophagogram showing a decrease in size of the esophagus toward normal. Usually the dilated esophagus does not diminish in size after either medical or surgical treatment.

be performed before irreversible changes have occurred in the cardiopulmonary systems.

Case 5. A 56-year-old man was first examined here on July 19, 1954. His presenting complaint was dyspnea that had its onset four years previously. Four months before initial examination here, the patient noted edema of the ankles, and shortness of breath at rest after prolonged talking. During the month before examination, he had several episodes of paroxysmal nocturnal dyspnea.

The history revealed the following information: at 11 years of age, he received a blow to the epigastrium which caused pain and abdominal distention for a short time; at 18 years of age, he first noted difficulty in swallowing which subsequently progressed until he could eat only soft foods and liquids; at 32 years of age, surgery was advised for achalasia and mega-esophagus but was refused; and at 34 years of age, he had syphilis. At 52 years of age, two episodes of severe upper-gastrointestinal bleeding occurred. Roentgen examination at that time showed mega-esophagus and duodenal ulcer, and surgery again was advised and refused.

B

A

Fig. 5. (Case 5) **A.** Roentgenogram of chest, showing enlargement of the esophagus extending beyond the enlarged border of the right side of the heart. **B.** Esophagogram showing a greatly enlarged and tortuous esophagus.

On physical examination the blood pressure was 118/80 mm. Hg, and the pulse rate was 96 per minute. The anteroposterior diameter of the chest was found to be increased and there were dullness at the bases of both lungs and many râles and rhonchi throughout both lungs. The heart was questionably enlarged and there was a loud presystolic gallop at the apex. Two-plus pitting edema of the ankles was present.

On laboratory examination the complete blood count, blood sugar level, serologic tests for syphilis, blood urea, and urinalysis were normal. Roentgen study of the chest showed pronounced enlargement of the esophagus with food and fluid levels extending far into the right pulmonary field. The pulmonary fields showed some fibrosis at both bases. Barium swallow showed gross dilatation of the esophagus to approximately 8 cm. in diameter with associated tortuosity (Fig. 5). After about two hours, two thirds of the barium still remained in the dilated esophagus. An electrocardiogram showed myocardial changes.

The patient refused to be hospitalized, so he was given medical treatment that consisted of a low-sodium diet, digitalis, and frequent mercurial injections.

During the first two weeks of treatment, the patient lost 15 pounds in weight. When the patient was last examined in June 1956, two years after initial examination, he still became short of breath after any exertion and frequently required diuretics. It was believed that this patient had pulmonary fibrosis with cor pulmonale and congestive failure and that the impairment of pulmonary and cardiac reserve contraindicated major operation.

Comment: This patient had a 38-year history of untreated achalasia that resulted in episodes of aspiration pneumonitis, and irreversible pulmonary fibrosis and emphysema, chronic cor pulmonale, and right cardiac failure. His condition illustrates the severe pulmonary and cardiac changes that can result from achalasia. Adequate medical treatment with dilations, diet, and other measures, at the onset of the achalasia might have prevented the pulmonary and cardiac changes. If dilations had been unsuccessful in controlling his symptoms, surgical treatment before the pulmonary and cardiac changes had become irreversible, probably would have been effective. Whether the blow to the abdomen or the syphilitic infection were etiologic factors in the achalasia is not known.

Summary and Conclusions

Achalasia, the failure of relaxation of the esophageal cardia, is associated with varying degrees of mega-esophagus, and should be regarded as a disease of the whole esophagus since primary peristaltic waves usually are absent throughout its entire length. The etiology of achalasia is unknown, but the condition frequently is associated with degeneration of Auerbach's plexus; it has been experimentally reproduced in cats by high vagotomy, and it has been reported to be clinically associated with deficiency of vitamin B_1.

The diagnosis is based upon: (a) history of food lodging in the lower esophagus, retrosternal pain, loss in weight, malnutrition, anemia, and regurgitation; (b) roentgen findings of diffuse dilatation of the esophagus tapering to a smooth constriction at the cardia, with a loss of primary peristaltic activity; and (c) esophagoscopic findings confirming the roentgen findings and excluding other disease.

The treatment of achalasia is primarily medical, chiefly through dilation of

Fig. 5. (Case 5) **A.** Roentgenogram of chest, showing enlargement of the esophagus extending beyond the enlarged border of the right side of the heart. **B.** Esophagogram showing a greatly enlarged and tortuous esophagus.

the cardiac sphincter. Supplementary measures include diet, vitamin B, sedation, and other drugs. Surgery is indicated only in patients whose conditions do not respond to medical treatment, and who develop regurgitation and aspiration pneumonitis, persistent anemia and malnutrition, and persistent severe pain. The dilated esophagus rarely returns to normal size after either medical or surgical treatment.

The reports of five cases are presented which demonstrate the diagnostic findings, the treatment, and some of the complications of achalasia. The first patient received only one dilation, and has remained essentially asymptomatic for six years since treatment. The second patient received several dilations, and has remained asymptomatic and has gained 95 pounds in weight during the seven and one-half years since the original dilation. The third patient who had a ten-year history of dysphagia, has remained asymptomatic for five years since one dilation was performed. The results in these three patients demonstrate that the symptoms of achalasia can be alleviated by medical treatment, including esophageal dilation.

Despite medical treatment including dilations, the fourth patient continued to have symptoms (chest pain, regurgitation, coughing, and aspiration pneumonitis), and a linear myotomy was performed. She has remained asymptomatic for one and one-half years after operation. The fifth patient had had achalasia for 38 years, and repeatedly had refused either medical or surgical treatment. He developed some of the complications associated with long-standing untreated achalasia: a large mega-esophagus, regurgitation, aspiration pneumonitis, pulmonary fibrosis, and chronic right cardiac failure thought to be associated with the chronic pneumonitis. It was believed that because of the chronic cardiac failure, he would not survive any major surgical procedure.

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DEFORMING POLYARTHROPATHY WITH EXCESS DEPOSITION OF CHOLESTEROL

Report of a Case

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THE accumulation of cholesterol in rheumatoid nodules is well recognized.[1-4] However, there heretofore has been no report of deforming polyarthropathy in association with cholesterol in nodules and, in addition, with cholesterol-containing pleural and joint effusions, deposition of cholesterol in synovial membranes, and normal concentration of serum cholesterol. The above-mentioned lesions and mild hepatic cirrhosis of the postnecrotic type occurred in a patient who will be described and discussed in this report.

Case Report

A 54-year-old white man had been in good health until the age of 39 years when, after a severe, acute, infectious illness that had been diagnosed as pericarditis with effusion, he developed severe pain with redness, warmth, and swelling in nearly all of the joints. The acute illness subsided within six weeks, but joint manifestations persisted and were characterized by exacerbations and remissions that resulted in synovial and periarticular thickening, tendon contracture, ankylosis, subluxations, and atrophy of adjacent muscles of the hands, wrists, elbows, knees, ankles, and feet. He had been unable to work since the onset of illness in 1939.

Ten years after the onset of illness (1949) he was first admitted to the Cleveland Clinic Hospital. At that time he had pain, swelling, and tenderness of the fingers, wrists, elbows, shoulders, jaws, ankles, and feet, and mild blurring of vision. Extension of both wrists was limited to 20 degrees and there was a 15-degree flexion deformity of the right elbow. Moderate effusion was present in each knee joint and there was pain on motion. Nodules were present over the extensor surfaces of the wrists, elbows, and sacrum. The eyes showed mild patchy injection of the bulbar conjunctivae bilaterally, which was thought to represent scleritis. A roentgenogram of the chest revealed multiple nodular densities throughout both lung fields and a pleural reaction at the base of the right lung, associated with effusion (Fig. 1). Thoracentesis produced 650 ml. of cloudy yellow fluid

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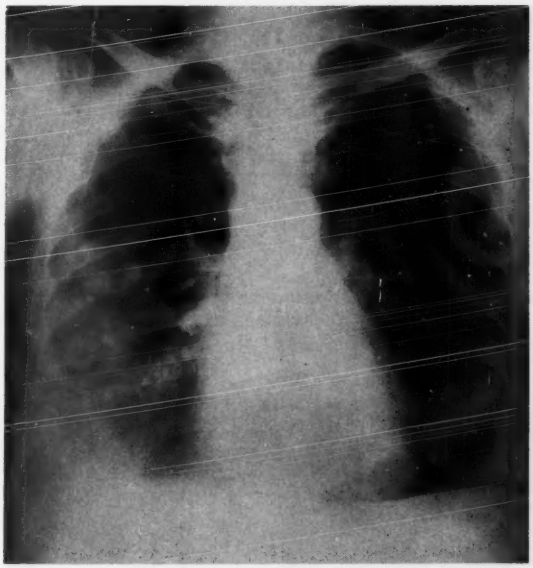


Fig. 1. Roentgenogram of chest in 1949.

that contained cholesterol crystals and fat globules. The protein content was 2.6 gm. per hundred milliliters. Direct smears and cultures were negative for tubercle bacilli and other organisms. Skin tests for histoplasmosis and coccidiomycosis were negative. The tuberculin skin test (Purified Protein Derivative #1) was positive.

Other laboratory findings were as follows: Blood hemoglobin 11.0 gm. per hundred milliliters; red cell count 4,140,000 and white cell count 4,300 per cu. mm. with a differential count of 58 per cent neutrophils, 37 per cent lymphocytes, and 5 per cent eosinophils. No abnormalities were noted on routine urinalysis. The total serum protein was 7.1, with albumin 2.6 and globulin 4.5 gm. per hundred milliliters. Blood urea content was 13.6, blood uric acid 2.5, serum calcium 13.2, and serum phosphorus 3.5 mg. per hundred milliliters. Serum cholesterol was 136 mg. per hundred milliliters, and sedimentation rate was 0.45 mm. per minute (Rourke-Ernstene method[5]). Treatment consisted of physiotherapy and sodium salicylate 4 to 6 gm. daily. He was discharged from the hospital with minimal objective improvement.

On January 4, 1955, he was readmitted to the hospital because of progression of the arthritis and failing vision. At this time he was able to walk only short distances in the house. Mild activity resulted in swelling of both knees and the right ankle. In addition to the failing vision he noticed yellow plaques in both sclerae that were increasing in size. A mild, morning cough productive of a small amount of white sputum first appeared in the summer of 1954, and it persisted to the time of this examination. Exertional dyspnea, present for years, had increased during the past year.

Physical examination revealed a man who appeared chronically ill. The skin was pale except for bilateral palmar erythema. The conjunctivae were injected bilaterally

and elevated with large yellow plaques that extended to within 2 mm. of the limbus. Slit-lamp examination revealed an irregular ring of corneal opacities from the limbus to 2 or 3 mm. into the cornea. Superficial and deep vascularization was present. The fundi revealed many fine vitreous floaters in the media. The discs were flat and of good color. There was diminished expansion of the chest bilaterally with dullness and decreased breath sounds at the base of the left lung. Dullness and absence of sounds were noted over the lower two thirds of the right lung field. Examination of the heart revealed the left border of cardiac dullness to be 8.0 cm. from the midsternal line. Heart tones were normal. The veins were flat and the peripheral pulses were full and equal. There was one-plus pitting edema of the feet and ankles. The pulse rate was 100 per minute and regular, and the blood pressure was 110/70 mm. Hg. The liver was smooth and was palpated 3 cm. below the right costal margin in the midclavicular line. The spleen and kidneys were not palpable. Advanced arthritic changes, manifested by subluxation and ulnar deviation of the fingers, and almost complete ankylosis of both wrists with interosseous atrophy were present (Fig. 2). There were 15-degree flexion contractures of

Fig. 2. Advanced arthritic changes and multiple nodules in the hand and wrist, 1955.

both elbows, and nodules were present on the extensor surfaces of both elbows and wrists. There was pronounced synovial thickening of both knees with bilateral effusion and severe atrophy of both quadriceps muscles. Both ankles were tender to light pressure, and moderate periarticular swelling was noted. There was tenderness, moderate synovial thickening, and subluxation of the metatarsal phalangeal joints. The dorsolumbar spine was almost completely ankylosed, and nodules were present over the sacrum.

A roentgenogram of the chest on January 5, 1955, revealed rounded nodular densities scattered throughout both lung fields; the densities were in the same distribution as they had been in 1949, although they appeared slightly smaller and contained areas of calcification (Fig. 3). There was some increase in size of the density in the lateral part of the base of the left lung. The density at the right costophrenic angle was unchanged. Roentgenograms of both knees showed pronounced narrowing of the joint spaces with evidence of demineralization, as well as localized erosion and cystic changes, adjacent to the articular cortex (Fig. 4). The wrists were markedly demineralized and there was nearly

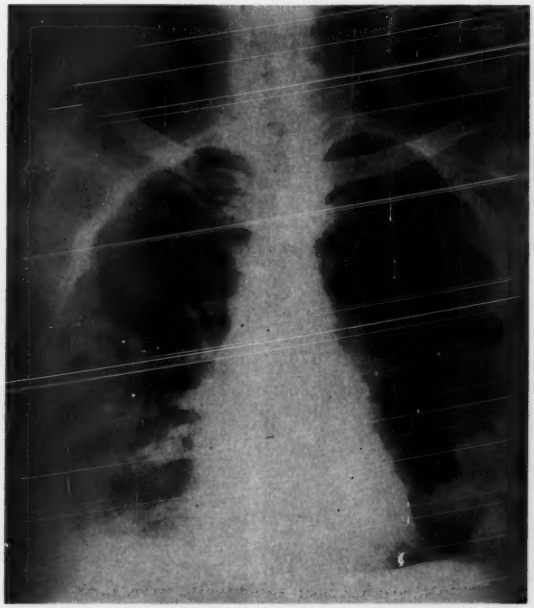


Fig. 3. Roentgenogram of chest in 1955.

complete obliteration of both joint spaces with localized erosion of the articular surfaces of each radius. Extreme flexion deformity of the hands with partial subluxation between the metacarpal and phalangeal bones was present (Fig. 5). A roentgenogram of the lumbar spine revealed hypertrophic changes of the lumbar bodies with partial collapse of L-2, which had not progressed since 1949. There were narrowing and sclerosis of the left hip joint and cystic changes in the femoral head, which had increased considerably since 1949.

An electrocardiogram was interpreted as showing myocardial changes. There were sinus rhythm and depression of RS-T in standard leads 2 and 3, aVF, V5, and V6. T waves were inverted in standard leads 2 and 3, aVF, and V6; diphasic in V4 and V5; and upright in aVR.

Laboratory findings were as follows: blood hemoglobin content 13.4 gm. per hundred milliliters; red cell count 4,900,000 and white cell count 4,500 per cu. mm., with 64 per cent neutrophils, 32 per cent lymphocytes, and 4 per cent eosinophils. A sedimentation rate was 1.3 mm. per minute (Rourke-Ernstene method). Urine specific gravity was 1.008, and tests for sugar and albumin were negative. Cholesterol crystals were not found microscopically in the urine. Blood urea content was 33, serum calcium 10.4, serum phosphorus 3.1, and serum cholesterol 130 mg. per hundred milliliters. Serum alkaline phosphatase was 3.5 Bodansky units, thymol turbidity was 4.5, and zinc sulfate turbidity was 6.8 units. Total serum bilirubin was 0.59 mg. per hundred milliliters. Cephalin cholesterol flocculation was negative at 48 hours. Prothrombin time was 14 seconds, or 100 per cent, and serum polysaccharides were 180 (normal 160) mg. per

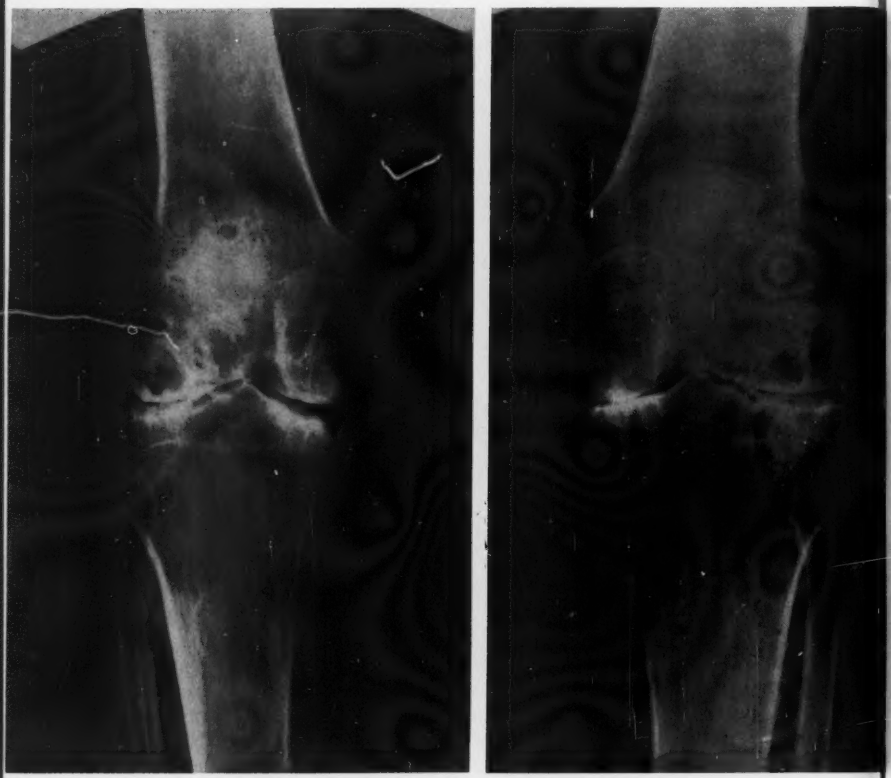


Fig. 4. Roentgenograms of knees in 1955.

hundred milliliters of blood (Shetlar method[6]). A plasma test for lupus erythematosus was negative.

On January 7, three days after the patient had been admitted, the total plasma protein content was 6.40 gm. per hundred milliliters by the biuret method. Electrophoretic analysis showed that the albumin was 3.28 (51.3 per cent of total proteins), alpha globulin 0.80 (12.5 per cent of total proteins), beta globulin 1.03 (16.1 per cent of total proteins), gamma globulin 0.84 (13.1 per cent of total proteins), and fibrinogen 0.43 gm. per hundred milliliters (7 per cent of total proteins).

Four hundred milliliters of turbid yellow fluid with masses of yellow flocculant precipitate was aspirated from the right knee. The fluid had a cholesterol level of 400 mg. per hundred milliliters with cholesterol esters of 211 mg. per hundred milliliters, and numerous cholesterol crystals were present.

A Vim-Silverman needle biopsy of the liver revealed old, slight cirrhosis that was compatible with the postnecrotic type. Histologically there was a slight-to-moderate

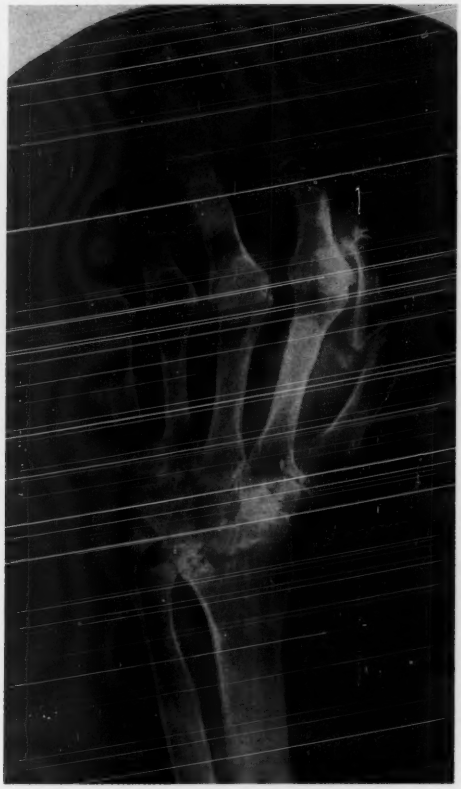
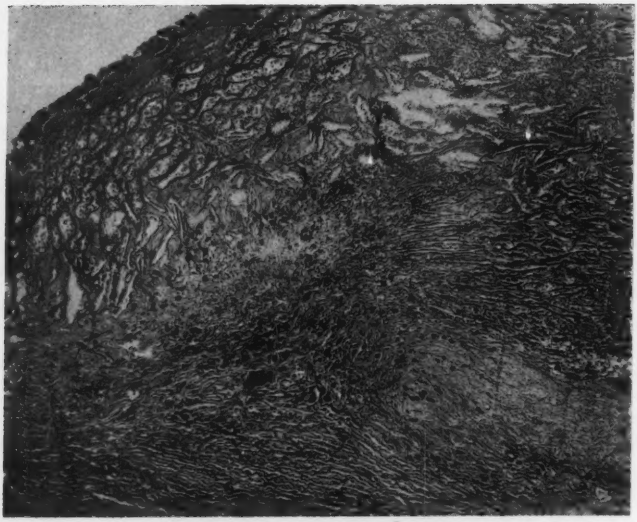


Fig. 5. Roentgenogram of the hand and wrist showing the advanced arthritic changes in 1955.

increase in connective tissue, principally in portal areas, and at least in one instance adjoining a central area. The involved portal zones were of irregular configuration but mostly were sharply demarcated from adjoining hepatic parenchyma. One focus of fibrosis showed slight extension of the fibrous tissue between hepatic cell cords. There was slight and somewhat focal infiltration of lymphocytes in areas of fibrosis. The hepatic cells were well preserved, and had a slightly pale, granular appearance that indicated normal glycogenation. No lipophages were evident.

Synovial biopsy specimens of the right knee and of the right wrist were obtained. Histologic sections (Fig. 6) revealed that portions of synovial membrane were formed externally by dense hyaline connective tissue with occasional foci of inflammatory cells, principally lymphocytes, but with some plasma cells and occasionally with histiocytes and a few neutrophils. The narrower, inner zone was comprised of less dense, at times finely fibrillar connective tissue and areas of degenerating and necrotic connective tissue, which was evident as ill-defined, granular, pink- or bluish-staining material containing



6a

6b

Fig. 6. Joint membrane. **(a)** Clefts (cholesterol) in zone bordering lining surface; X90. **(b)** Degenerating collagen, clefts (cholesterol), and hypercellular area with histiocytes and giant cells; X200. **(c)** Lining membrane covered with unorganized material containing clefts (cholesterol) and infiltrated by histiocytes, lipophages, and giant cells; X270.

6c

scattered cleftlike clear spaces (cholesterol). Histiocytes, vacuolated macrophages (lipophages), and giant cells, occasionally of Touton type, were present singly or in small groups adjoining some of the areas with the cleftlike spaces. The acellular, degenerated areas were in part imperfectly marginated by an ill-defined zone of fibroblasts and histiocytes, which at times were more distinct than others, but without true palisading. The lining surface was formed in patches by a fibrinoid layer of irregular thickness, focally containing small, cleftlike spaces. Synovial epithelial cells were not evident in any section.

A nodule was removed from the dorsum of the right hand. Histologically (Fig. 7) this was formed centrally by necrotic collagenous connective tissue in which the hazy outlines of collagen bundles were in part evident and also areas in which the precedent structure could not be identified since there was only a granular pink-staining material present. Areas in the central necrotic portion contained cleftlike spaces (cholesterol). The phosphotungstic acid—hematoxylin stain revealed dense patches of dark purple-staining fibrin-like material. The outer portion of the nodule was formed by dense collagenous and hyaline connective tissue, with hypercellular zones of fibrocytes, histiocytes, and lipophages, most apparent immediately adjoining the zone of central degeneration, producing a somewhat palisaded appearance. There was no evidence of old hemorrhage. In one area at the junction zone there was a microscopic focus of liquefaction necrosis, marginated by fibrinoid and bluish-staining material. Blood vessels in the loose areolar tissue immediately adjoining the nodule showed a pronounced but focal adventitial infiltration by lymphocytes and a few neutrophils.

b

a

Fig. 7. Nodule from dorsum of hand. **(a)** Acellular zone with central area of necrosis, clefts (cholesterol), and peripheral collagen; X80. **(b)** Another area showing degenerating collagen and hypercellular periphery; X270.

Eleven months later, in December 1955, the patient was re-examined. The joint involvement was unchanged and a mild effusion of the right knee persisted. The serum cholesterol content was 126 mg. per hundred milliliters of blood. A roentgenogram of the chest revealed the same atypical parenchymal and pleural changes with no significant difference from previous films.

Discussion

It is well recognized that under certain conditions excess accumulation of cholesterol may occur in various body cavities while the serum cholesterol remains normal. Cholesterol-containing pericardial effusion may accompany myxedema or may occur as a result of tuberculous pericarditis or hemopericardium.[7] Cholesterol-containing pleural effusion has been reported to be associated with tuberculosis, diabetes, syphilis, and metastatic adenocarcinoma of the lung and pleura.[8-11] Neither pericardial nor pleural cholesterosis has been reported in association with deforming polyarthropathy.

Although the etiology of the pulmonary lesions has not been determined, it is reasonable to assume that the pleural effusion is directly associated with the pulmonary lesions. The pulmonary nodular lesions probably are not malignant, inasmuch as no appreciable change could be identified roentgenographically during the past six years. Tuberculosis was considered an etiologic possibility, although numerous sputum examinations and cultures of gastric washings have been negative for tubercle bacilli. The roentgen appearance of the pulmonary lesions and the positive skin test (Purified Protein Derivative # 1) contraindicated sarcoidosis. Pulmonary xanthomatosis also was considered because it can occur as granulomatous nodular infiltration or as solitary xanthomas.[12-15] However, while bone and tendon lesions may occur, advanced deforming polyarthritis has not been reported in xanthomatosis; it would be most unusual for the pathologic changes in the joints and the lungs to be unrelated while both are characterized by excess accumulation of cholesterol.

According to Horwitz,[4] rheumatoid nodules when stained with scarlet red, histologically show a high incidence of lipid and a variety of lipid changes have been described. He has attempted to simplify the problem by postulating that the primary change is the deposition of a small amount of cholesterol or other lipid in the central necrotic area, and that the subsequent appearance of a nodule probably depends to a great extent on the site of deposition, the amount of lipid that is deposited, and the reaction of the surrounding tissues to the presence of the lipid. This postulation would explain the presence of cholesterol crystals or other lipid material in varying amounts extracellularly, and the presence of foam cells containing lipids in variable amounts intracellularly, resulting in various histopathologic appearances. The presence of lipid is not limited to rheumatoid arthritis but may occur in gouty arthritis. Kersley, Gibson, and Desmarais[2] have noted the presence of cholesterol crystals and foam cells in tophi of gouty patients.

Horwitz[4] suggested that the subcutaneous nodules of rheumatoid arthritis

with lipid deposition that have been described are not distinct entities but merely are different histopathologic end results of a process with a common pathogenesis, that is, the deposition of lipid in the necrotic foci in the nodules. This may be the case, still, the manner in which lipid is deposited in the necrotic areas remains unknown.

Fletcher[1] described a case of rheumatoid arthritis in a 42-year-old man who had widespread necrosis of numerous subcutaneous nodules, cellular proliferation, round-cell infiltration, and vascular lesions in these nodules. The presence of cholesterol was demonstrated in the areas of necrosis surrounded by foam cells; the serum cholesterol remained normal. Layani reported a case, reviewed by Horwitz,[4] which was similar to ours except that the patient was a 46-year-old woman with deforming arthritis of 15 years' duration. She developed xanthoma planum et tuberosum, angina, jaundice, hepatomegaly, and hypercholesteremia. Autopsy was not performed, but Thannhauser[12] believes that this patient's condition probably was a coincidental combination of rheumatoid arthritis with generalized primary xanthoma and xanthomatous biliary cirrhosis.

The hepatomegaly and the histopathologic findings on liver biopsy in our patient are interesting and not easily or readily explained. Possibly hepatitis without jaundice had occurred previously, although the history failed to confirm this suspicion. Or it is possible that the disease, because of its generalized and widespread distribution, also involved the liver, which later healed with residual fibrosis and scarring.

Accumulation of lipid, such as cholesterol, in certain serous cavities apparently is a nonspecific reaction, since it is not limited to single sites or to specific diseases. Thus, cholesterol deposition in some cases may be minimal and localized to a single solitary inflamed bursa, and in others may be increased in amount and distribution so as to involve the pleural or the pericardial sac or both, and, as in the present case, nodules, joints, pleurae, and conjunctivae.

It is unlikely that the cholesterol accumulations in the case reported here are attributable to transport of excess lipid to the affected areas, since the serum cholesterol concentration always has been normal or low. Rather, since fibrous tissues, such as in the aorta, are capable of cholesterol synthesis, [16] it may be that this synthetic mechanism can be locally accelerated or that the mechanisms of destruction or transport of cholesterol can be locally suppressed. Again, it may be that local factors act in such a way as to promote deposition of free cholesterol from cholesterol that was transported to the joint or formed locally at normal rates. Any of these circumstances, to the extent that they would result in formation of crystalline cholesterol, would remove the cholesterol from effective contact with mechanisms that normally transport or destroy cholesterol so that the accumulation, after it had started, would tend to increase with time. In an attempt to analyze which of these various mechanisms may be at fault in this case, studies of local cholesterol metabolism are planned.

Summary

An unusual case is reported in which deforming polyarthropathy is associated with extensive cholesterosis involving nodules, pleural and synovial membranes, conjunctivae, and probably the lungs.

Mesenchymal cholesterosis appears to be nonspecific and not limited to a single disease.

The mechanism of accumulation of free cholesterol is not known.

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COMMERCIAL GLUCOSE OXIDASE PREPARATIONS FOR THE DETECTION OF GLUCOSE IN URINE

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ALTHOUGH enzymes which oxidize glucose are abundant in nature and have been known for many years, until recently, no application of their activity has been made in clinical biochemistry. The first enzymatic preparation with specific glucose oxidase activity was described by Müller[1] in 1928. Subsequent workers have isolated other preparations. The best known of these enzyme preparations is *notatin*, which Coulthard and associates[2] isolated from *Penicillium notatum* and described in detail in 1945. These enzymes are flavoproteins, and they catalyze the aerobic oxidation of glucose to gluconic acid with the production of hydrogen peroxide.

Recently there have appeared on the market two commercially prepared glucose oxidase reagents, Clinistix* and Tes-Tape,** which are designed to detect the presence of glucose in urine by color changes of reagent-treated paper. Each of these preparations is specific for glucose and no heating is required to bring about the reaction. This fresh approach to the detection of glucose after more than a century of exploitation of copper reduction by glucose seemed to warrant clinical trial of these two new preparations. Our report presents the results of a clinical trial, and evaluates both the new preparations and the conventional solution with respect to sensitivity, specificity, convenience, and economy.

Materials and Methods

The standard Benedict's technic used in our laboratory involves the use of Benedict's solution prepared from precompounded Benedict's reagent†. Five milliliters of reagent and 5 drops of urine are mixed and boiled for 5 minutes in a water bath. At the end of that time, readings are taken and are expressed in the usual semiquantitative manner as negative, or from (+) to (++++). Determinations of urinary sugar on a specimen showing (+++) reactions had a reducing sugar content of approximately 1 per cent as measured by the quantitative Benedict's procedure. This suggests that the method as we do it compares well with the manner in which it is carried out elsewhere.

Clinistix reagent strips consist of 2½-inch strips of heavy filter paper mounted like matches in a paper folder. Only the ends of the matchlike strips

Clinistix, reagent strips: Ames Company, Inc., Elkhart, Indiana.
**Tes-Tape, urine sugar test tape: Eli Lilly & Company, Indianapolis, Indiana.*
†Purchased from the Paragon Test Laboratory, Orange, New Jersey.*

are impregnated with active material. To test urine for glucose, a strip is torn from the folder, the impregnated end of the strip is dipped into the urine specimen and is allowed to develop color. The reaction is not quantitative because in different specimens of urine many factors, including acidity, alkalinity, temperature, and amount of inhibitory substances, affect reactions of enzymes. The minimal concentration of glucose detectable by Clinistix ranges from as little as 0.01 per cent to 0.1 per cent, depending upon the amount of inhibitory substances present in the individual urine specimen. Thus, the color change is not proportional to the concentration of glucose in the urine.

Tes-Tape is a special paper impregnated with the enzymes, glucose oxidase and a horse radish peroxidase, in addition to an oxidizable substrate, ortho-tolidine. In the presence of glucose and moisture, the glucose oxidase reacts with the hydrogen peroxide and ortho-tolidine to develop a color in 60 seconds ranging from light green to blue-black, depending upon the concentration of glucose present. Tes-Tape is dispensed as a long roll of paper in a plastic dispenser similar to that used with many pH papers. A color scale is included which shows the different colors to be expected with increasing concentrations of urinary glucose. However, Tes-Tape does not distinguish in the important

Table 1. — *Results of 1340 parallel determinations using Clinistix and Benedict's reagent*

Type of test and result	No. of specimens
Both tests negative	1264
Both tests positive	56
Only Clinistix positive	20
Only Benedict's positive	0
Total	1340

Table 2. — *Results of 1000 parallel determinations using Benedict's reagent, Clinistix, and Tes-Tape*

Type of test and result	No. of specimens
All tests negative	945
All tests positive	38
Only Benedict's positive	0
Only Clinistix positive	1
Only Tes-Tape positive	4
Both papers positive, Benedict's negative	12
Total	1000

range between ½ per cent (+++) and 2 per cent or more (++++) of urinary glucose.

The first group of 1340 routine specimens of urine was subjected both to the Benedict's test and to the Clinistix test. The results of these tests are shown in Table 1. A short time after the completion of this series, Tes-Tape became available to us, and Table 2 shows the results of tests of 1000 routine specimens of urine using Clinistix, Tes-Tape, and Benedict's solution.

Comparison of Tests

Sensitivity. From these data, it is apparent that the sensitivity of the test papers is greater than that of our standard Benedict's test. Review of the charts of 15 patients from whom specimens were collected which gave positive oxidase and negative Benedict's tests indicated that the most common diagnosis was diabetes mellitus (10 patients). Other diagnoses included anxiety and nervous tension states (3 patients); back strain, arteriosclerotic cardiac disease, malignant glioma (1 patient each). Fasting blood sugar determinations on specimens from the five nondiabetic patients ranged from 65 to 85 mg. per hundred milliliters.

Specificity. The oxidase tests have the advantage of distinguishing glucose from other reducing substances in the urine, but no specimens are included in the present series in which a nonglucose-reducing sugar was present. A specimen in which this question was raised was sent to our chemistry laboratory and was submitted to the oxidase preparations to determine the nature of the reducing substance present. In this instance, both of the oxidase tests suggested that the reducing sugar was glucose. The oxidase in each of the preparations is specific, and negative tests were obtained with specimens of urine to which had been added lactose, fructose, zylose, or mannitol. A wide variety of drugs including acetylsalicylic acid, d-amphetamine, barbiturates, sulfonamides, quaternary ammonium compounds, and hexylresorcinol did not affect the reaction.

To compare further the specificity of the three tests, two normal persons were given 50 gm. of glucose by mouth, which is half the usual dose administered for the glucose tolerance test. In the one individual no glucose was found by the copper reduction or oxidase tests. However, for the other subject the glucose oxidase tests were positive at 15 minutes and at one and at two hours, although the Benedict's tests had been negative. Attempts to produce alimentary glycosuria, as measured by the oxidase paper tests, in this person by having him ingest high-carbohydrate food such as candy, failed even when the estimated amount of sugar eaten surpassed the 50 gm. Five patients submitted to glucose tolerance tests were studied by comparing the results of simultaneous tests of urinary excretion of glucose and the blood sugar levels. Among the urine specimens examined were three specimens that were negative to our standard Benedict's test and positive to the paper glucose oxidase tests. Determinations of blood sugar made at the time these specimens were collected ranged from 41 to 241 mg. per hundred milliliters.

Convenience and Economy. Under the conditions of the testing in our laboratory, the impregnated-paper preparations were not as convenient to use as the conventional qualitative Benedict's procedure. The manufacturers have designed the tests not particularly for use in the hospital laboratory but rather for small-scale use by the office technician or by the diabetic patient himself. In each paper method it is necessary to tear off the paper strips and to keep those individual bits of paper in order. We believe that this procedure is more complicated than the Benedict's test as it is performed in our laboratory. The three methods are about equally time consuming and, in view of their higher purchase price, it appears that each of the newer procedures would cost the hospital laboratory more per test than the copper-reduction method.

Of the two new products Clinistix was easier to use, while Tes-Tape was easier to read. The matchlike Clinistix papers were easy to dip into the urine specimens; whereas the Tes-Tape papers had a tendency to curl, making it necessary on occasion to use forceps for dipping the reagent paper into the urine. However, Tes-Tape is almost as quantitatively exact as is our Benedict's procedure, and it was made more convenient to use by first cutting the entire roll into strips and storing the small pieces of paper in a wide-mouthed glass-stoppered jar.

Summary

Clinical trial of two commercial glucose oxidase preparations shows them to be more sensitive in the detection of glucose in the urine than the conventional Benedict's test. The glucose oxidase preparations are not as convenient as the Benedict's test for large-scale testing; but, if their high sensitivity is taken into consideration, they are excellent products for use in the office laboratory, at the bedside, or by the diabetic patient himself. These reagents also are useful as reference tests in the determination of the nature of copper-reducing, non-glucose substances in urine because they are highly specific for glucose.

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CYSTIC CRANIOPHARYNGIOMA: SURGICAL TREATMENT BY ENDONASAL APPROACH

Report of a Case

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CRANIOPHARYNGIOMAS are benign pituitary tumors that arise from Rathke's pouch. These tumors usually are cystic, but may be solid. Many other names have been given to these tumors, including *Rathke's pouch cysts or tumors*, *hypophyseal duct cysts or tumors*, *suprasellar cysts or tumors*, *adamantinomas*, and *epitheliomas*. Craniopharyngiomas need not be difficult to diagnose, but they always are difficult to treat.

This report presents the case history of a patient whose cystic craniopharyngioma was treated by endonasal sphenoidostomy and aspiration of the tumor mass.

Report of Case

A 35-year-old Negro man was first seen at the Cleveland Clinic in December 1947. His chief complaint was loss of libido, which he had first noted five years earlier. His history revealed that, approximately three years before examination, while serving in the Armed Forces in October 1944, he had noted loss of vision in the lateral area of the left eye. A brain tumor had been diagnosed, and a right frontal craniotomy had been performed in 1945 in an Army hospital. After surgery the sight in the left eye had improved, but vision in the right eye had decreased. He had been unable to read or to distinguish the features of people, but he had been able to get around by himself. When he was initially seen at the Clinic, the diagnosis of impotence probably secondary to suprasellar tumor was made. Testosterone propionate, 25 mg. three times weekly for three weeks, and 50 mg. three times weekly for three additional weeks, was administered, without improvement in his condition.

Two and one-half years later (June 1950) he returned to the Clinic to be examined in the Department of Ophthalmology because of total blindness of sudden onset ten days previously, allegedly following an upper respiratory infection. He said that he occasionally had had an ache in the right eye but no headaches. On examination, there were dilation of the pupils, absence of light reflex, bilateral paralysis of the sixth nerve, pale optic discs bilaterally, and total blindness. Recurrent suprasellar tumor was suspected and he was referred to the Department of Neurological Surgery. Except for the previously mentioned ocular findings, the neurological examination was negative. A spinal tap was not contributory.

Roentgenograms of the skull (Fig. 1) showed destruction of the sella turcica with pronounced depression of the floor. The dorsum sellae turcicae and the posterior clinoids were not visualized. A small calcification was present in the midline, posterior to the region of the sella turcica. No other intracranial calcifications were demonstrated. The

sphenoid and petrous ridges appeared to be normal, but there was a 1 by 2 cm. defect in the left sphenoid wing, probably representing bone erosion. A bone flap was noted in the right frontal temporal region.

In June 1950 a left frontal craniotomy was performed, revealing a large cystic tumor beneath and anterior to the optic chiasm. Aspiration yielded approximately 60 cc. of dark oily fluid. A circular section of the cystic wall removed for histopathologic examination was reported to be fibrous tissue.

Four years later, in July 1954, the patient was seen in the Department of Otolaryngology with symptoms of hoarseness, dysphagia, and a tendency to choke on liquids, of one month's duration. The findings on examination were: a mass filling the nasopharynx, paralysis of the right hypoglossal nerve, paralysis of the right side of the soft palate, paralysis of the right vocal cord, and diminished gag reflex.

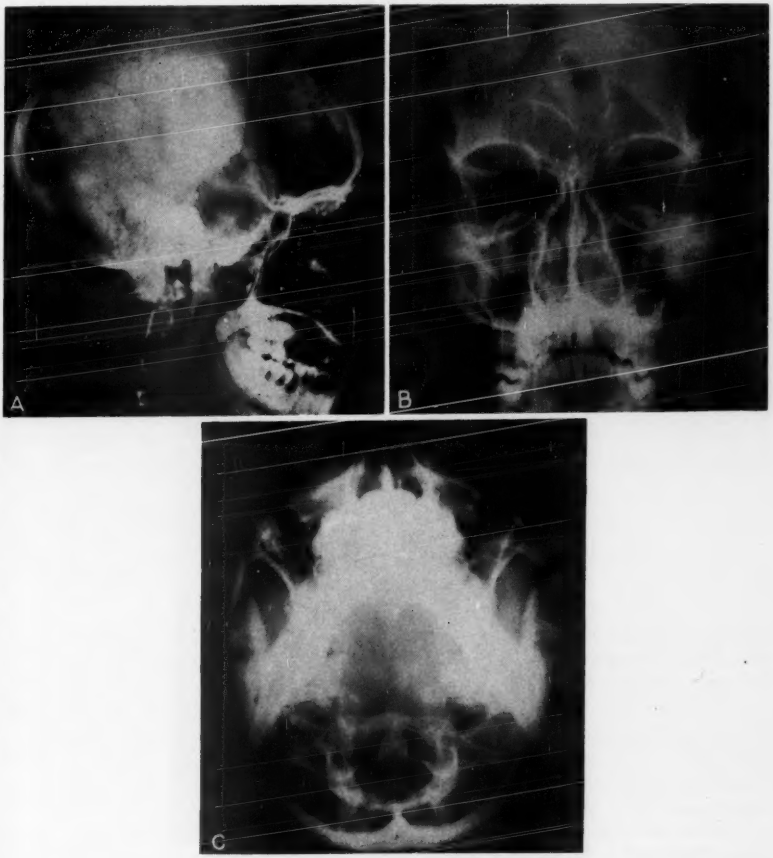

Fig. 1. Preoperative roentgenograms in 1950.

Roentgenograms of the skull at this time (Fig. 2) showed destruction of the floor of the middle fossa and calcification in a large area 5 cm. in diameter in the central region of the base of the skull. Part of this calcification was intracranial above the petrous tips, with the remainder in the nasopharynx extending down almost to the soft palate. The size of the nasopharyngeal tumor appeared to be greater than that indicated by previous roentgenograms in June 1950. The tips of the petrous apices were eroded.

In August 1954, an endonasal sphenoidostomy was performed. A transseptal approach was considered unnecessary because the nasal passages were large. The nasopharynx was well visualized by anterior nasoscopy after shrinkage and out-fracturing of

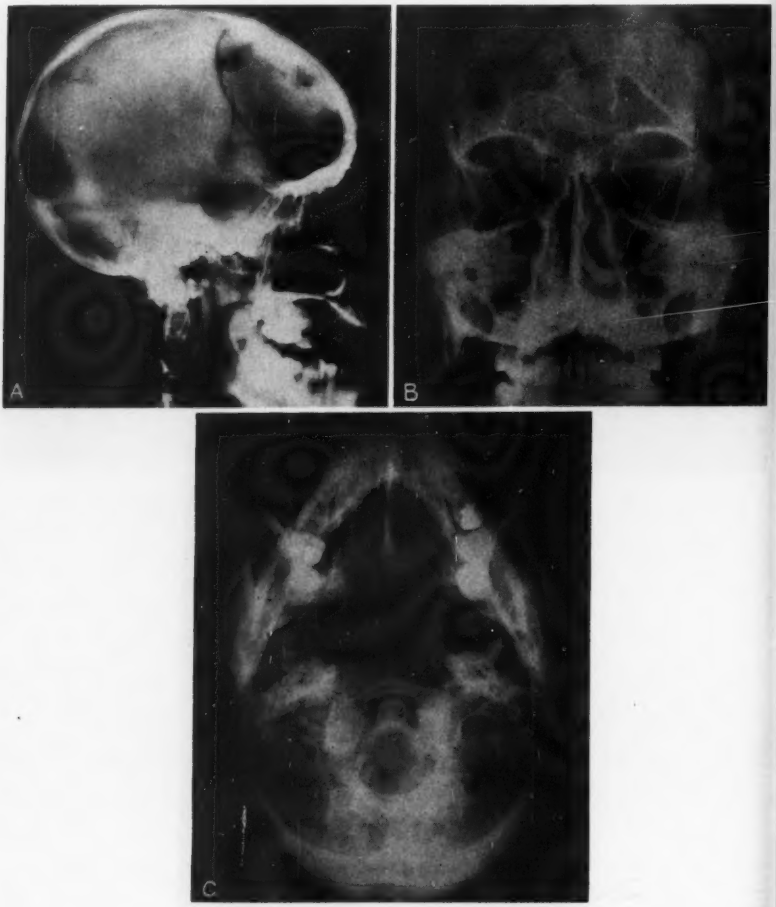

Fig. 2. Preoperative roentgenograms in 1954.

the turbinates against the lateral nasal wall. An incision was made (through the right nostril) into the tumor mass, releasing 70 to 80 cc. of dark-brown oily fluid. With a punch forceps the right nasal opening to the tumor was enlarged to approximately 2 cm. in diameter. A similar opening was then made through the left nostril, and the two openings were converted into a single large opening by removal of a portion of the posterior nasal septum (Fig. 3). (The procedure is similar to that described by Hirsch[1] which, however, entails submucous resection.)

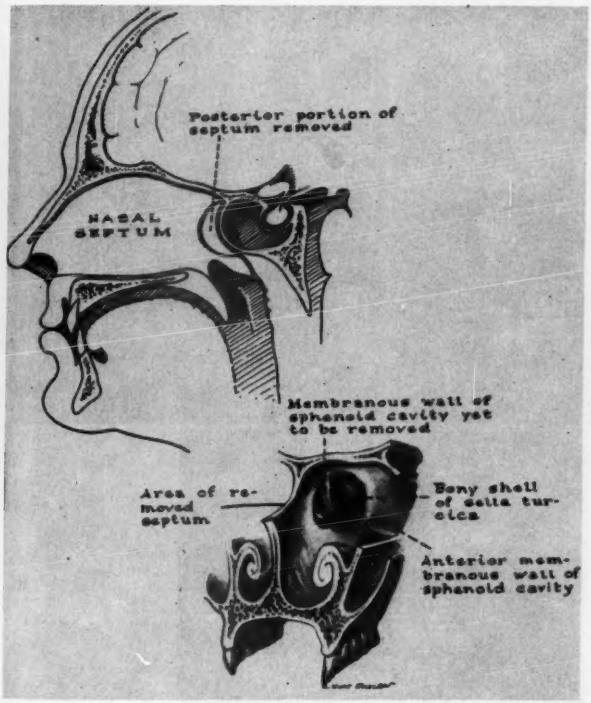

Fig. 3. Diagrams of operative technic.

The cavity was packed with 1-inch vaseline gauze. This pack was gradually removed during the next four days. On the fifth postoperative day roentgenograms obtained after instillation of 30 cc. of iodized oil outlined the cavity (Fig. 4). The immediately postoperative course was not remarkable.

Six months postoperatively, roentgenograms obtained after instillation of iodized oil showed a decrease in the size of the cavity (Fig. 5). In June 1955, nine months after operation, the patient said that his hoarseness had cleared and his tongue had been moving better during the past month. At that time he had normal movements of the tongue, a very active gag reflex (topical anesthesia had to be applied in order to visualize the larynx), normal movement of the soft palate, and good motion of the right vocal cord. The patient was last seen in December 1955, approximately 16 months after

surgery. The sphenoidal opening was patent and the patient stated that, except for his blindness and impotence, he felt better than he had in years.

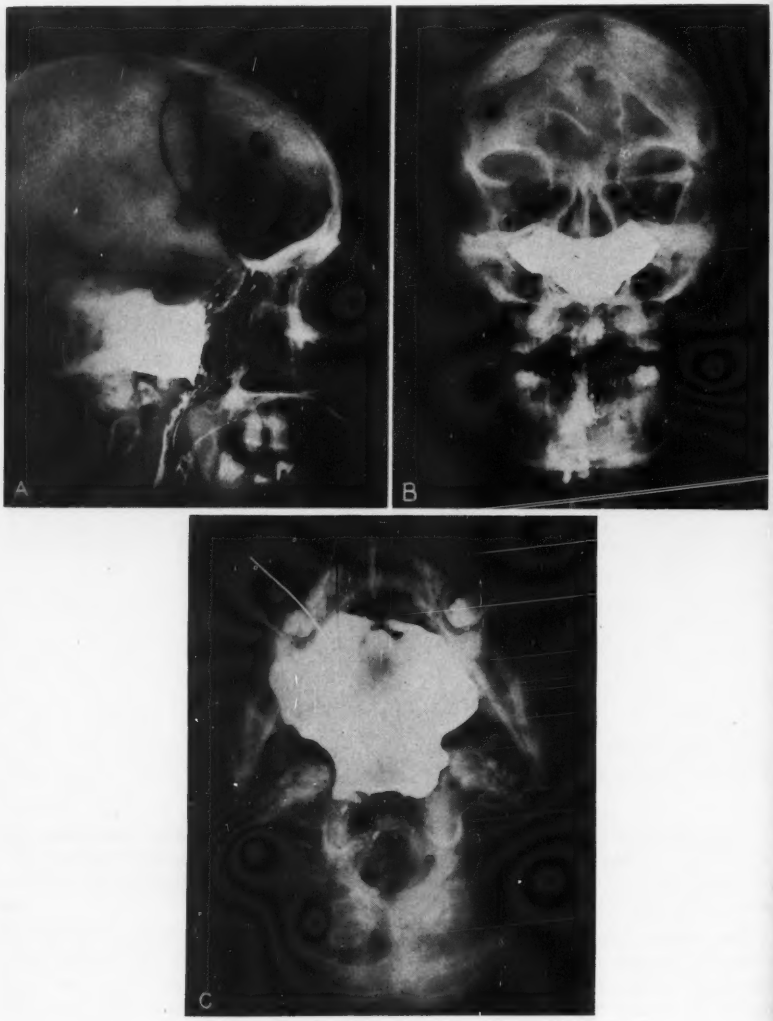

Fig. 4. Roentgenogram of cavity after instillation of iodized oil immediately after operation.

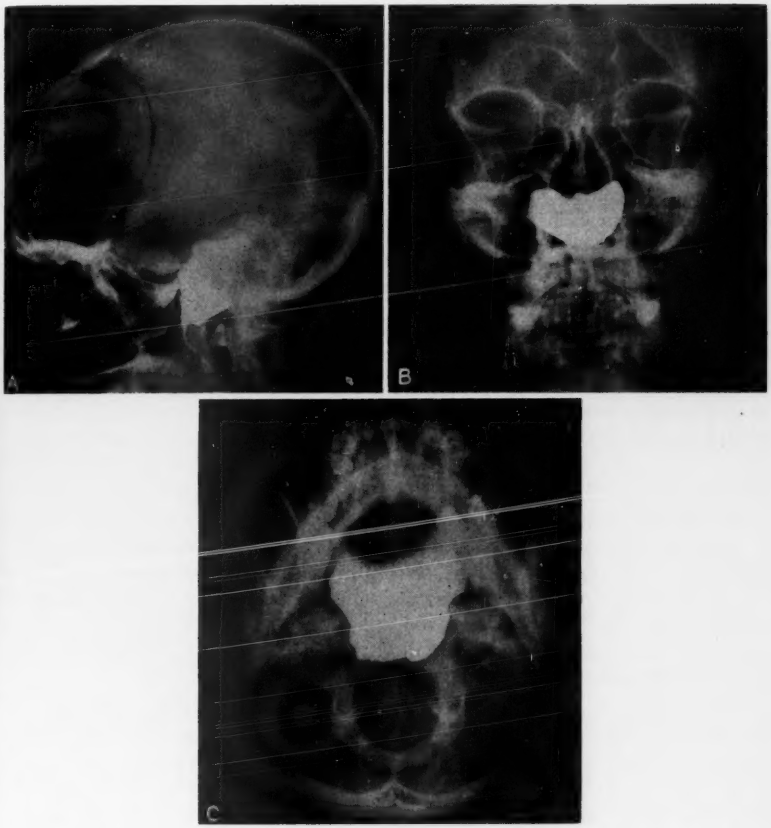

Fig. 5. Roentgenogram after instillation of iodized oil six months postoperatively.

Discussion

Diagnosis. The diagnosis of craniopharyngiomas like that of other pituitary tumors is made on the basis of endocrinologic, ophthalmologic, and roentgenographic findings. In the case presented, hemianopsia was the first symptom that caused the patient to seek medical aid, although he had noted a loss of libido two years earlier. Total blindness and paralysis of the extraocular muscles developed approximately five and one-half years after the onset of the hemianopsia. Roentgenograms of the skull at that time showed destruction of the sella turcica by a tumor mass with a partially calcified periphery, and thus probably indicative of a craniopharyngioma.

The occasional difficulties in diagnosing craniopharyngioma are exemplified by the results reported for one series of 96 patients who were operated upon for suspected craniopharyngioma and in 6 of whom no tumor was found.[2] Endocrine disturbances may not be apparent in children, who comprise a large proportion of persons having craniopharyngiomas, [2,3] or in menopausal or in hysterectomized women. An enlarged sella turcica is not in itself diagnostic since hydrocephalus or glioma in the region of the sella may cause the enlargement. Sphenoid mucocele,[4] a rare condition, also must be considered in the differential diagnosis. Calcifications considered characteristic of craniopharyngiomas also may be found in aneurysms, chondromas, osteomas, and sclerotic carotid arteries. Roentgenograms with contrast air filling and arteriograms may be of diagnostic aid.

Treatment. Craniopharyngiomas may be treated medically, surgically, and by irradiation. Medical management generally is instituted for the control of the endocrine disturbances. Irradiation alone has been considered of no value in treatment,[3] although postoperative irradiation has been reported to alleviate symptoms that had not been relieved by surgery or that had recurred postoperatively.[5] The surgical treatment employs either of two approaches: the transfrontal craniotomy, or the endonasal sphenoidostomy.

Gordy, Peet, and Kahn[3] reported a mortality of 41 per cent in a series of 51 patients having craniopharyngiomas operated upon by the transfrontal approach. They remarked on the pessimism among neurosurgeons concerning the results of surgery for craniopharyngiomas, occasioned by the high operative mortality and the many cases in which total removal is manifestly impossible. Love and Marshall[2] reported a mortality of 40 per cent in 96 patients after transfrontal craniotomy for craniopharyngioma.

Many variations of the transsphenoidal approach have been performed, but the one used most frequently, most successfully, and for the longest period of time is the transseptal-sphenoidal approach (nasal submucous resection route) devised by Hirsch.[1] From 1910 to 1951, Hirsch employed this procedure in the treatment of 383 pituitary tumors of various types, such as the chromophobic and eosinophilic adenomas where there was enlargement of the sella turcica, with about 35 per cent being cystic or semicystic tumors (craniopharyngiomas or cystic chromophobic tumors). Although he did not classify his data according to types of tumors, the over-all mortality for his series was significantly low—5.4 per cent. A very recent report by Hirsch,[6] analyzing a total of 413 patients with pituitary tumors, reveals a 1.5 per cent mortality in the antibiotic era since 1945. On the basis of these figures it would appear that selected pituitary tumors where there is enlargement of the sella turcica could be readily approached through the endonasal route.

Summary

A case report is presented of a patient with a cystic craniopharyngioma that had been treated by two transfrontal craniotomies without preventing continued

enlargement of the tumor and cranial nerve involvement. Aspiration of the neoplasm through endonasal sphenoidostomy resulted in recovery of the involved nerves. It is believed that the endonasal approach has definite application in the treatment of cystic craniopharyngiomas such as that in the case presented.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

affiliated with

THE CLEVELAND CLINIC FOUNDATION

announces Courses for the Academic Year 1956-1957

Current Therapy in Pediatric Practice (see page 227)
. . . . . September 26 and 27, 1956

Progress in Management of Rheumatic Diseases (see page 228)
. . . . . October 24 and 25, 1956

Blood Bank Management . . . . . November 15 and 16, 1956

Physics of Radiology (Thursdays 5:00 p.m.)
. . . . . January 3 through April 25, 1957

General Practice . . . . . February 6 and 7, 1957

Postgraduate Course in Otology, Rhinology, Laryngology, Maxillofacial Surgery, Bronchoscopy, and Esophagoscopy . . . . . February 27 and 28, 1957

Medical Progress and Its Relationship to Dentistry . . . . . March 13 and 14, 1957

Psychosomatic Aspects of Obstetrics and Gynecology . March 20 and 21, 1957

For further information
please write to

The Registrar
The Frank E. Bunts Educational Institute
2020 East 93 Street
Cleveland 6, Ohio

ANNOUNCEMENTS

CURRENT THERAPY IN PEDIATRIC PRACTICE

The Bunts Institute is sponsoring the fourth annual postgraduate continuation course in pediatries, **Current Therapy in Pediatric Practice,** presented by the Department of Pediatrics on September 26 and 27, 1956. Guest speakers will include James L. Wilson, M.D., Professor of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan; and Lawrence K. Pickett, M.D., Pediatric Surgeon and Associate Professor of Surgery, New York State Medical Center, Syracuse, New York.

The registration fee is $15.00. Reservations will be accepted at any time by the Registrar of the Bunts Institute. The course is limited to 150 registrants.

REGISTRATION FORM

THE REGISTRAR
THE FRANK E. BUNTS EDUCATIONAL INSTITUTE
Cleveland Clinic
2020 East 93 Street
Cleveland 6, Ohio

Please register me for the course *Current Therapy in Pediatric Practice*, to be given September 26 and 27, 1956. (Registration fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing a check for $5.00 and will pay the remainder on September 26. (Please make check payable to The Frank E. Bunts Educational Institute.)

Name . . . . . .

Address . . . . . .

Name of Medical School and
Date of Graduation . . . . . .

(*This course is open only to graduates of approved medical schools.*)

ANNOUNCEMENTS

PROGRESS IN THE MANAGEMENT OF RHEUMATIC DISEASES

The Bunts Institute is sponsoring a postgraduate continuation course in rheumatic diseases, **Progress in the Management of Rheumatic Diseases,** presented by the Department of Rheumatic Disease on October 24 and 25, 1956. The course is designed for physicians interested in various rheumatic diseases. The discussions will include recent and significant advances in the diagnosis and management of fibrous tissue disorders. Symposia and panel discussions in the areas of medical and surgical interest as they pertain to rheumatoid and gouty arthritis, rheumatic heart disease, lupus erythematosus, and periarteritis nodosa are planned. The session will close with a clinical demonstration of patients.

The principal guest speaker will be William D. Robinson, M.D., Professor of Medicine, University of Michigan Medical School, Ann Arbor, Michigan, and President of the American Rheumatism Association.

A final program of the course will appear in the October issue of this journal. For details of the program prior to publication please write to

The Registrar
The Frank E. Bunts Educational Institute
2020 East 93 Street
Cleveland 6, Ohio